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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/321,655	05/28/1999	STANTON L. GERSON	CWR-7091NP	6848

26294 7590 01/20/2012

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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
01/20/2012	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/321,655
Filing Date: May 28, 1999
Appellant(s): GERSON, STANTON L.

Richard A. Sutkus
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/16/2011 appealing from the Office action mailed 11/16/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 2-5 and 7.

(4) Status of Amendments

The examiner has no comment on the appellant's statement of the status of amendments contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

US 7,592,174	Sylvester et al.	9-2009
US 2002/0168765	Prockop et al.	11-2002

Prockop, D. J. "Marrow stromal cells as stem cells for nonhematopoietic tissues" Science, vol276 (4 April 1997), pp. 71-74.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(a) Claims 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995) as evidenced by Prockop, D.J. (Science 276:71-74, 1997) and/or Prockop et al (US 2002/0168765).

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by 4th passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells (Abstract, and column 1, page 102). **The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture** (column 1, third paragraph, page 102), and it contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (Science 276:71-74, 1997; see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages**" (see the abstract).

Therefore, the bone marrow stromal cells that were passaged 4 times for transduction as taught by Nolta et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue; and that the utilized cell population can be considered to be homogeneous because it is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture. Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Nolta et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Accordingly, the method taught by Nolta et al meets every limitation of the claims as broadly written. Therefore, the reference anticipates the instant claims.

(b) Claims 2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Wells et al. (Gene therapy 2:512-520, 1995) as evidenced by Prockop, D.J. (Science 276:71-74, 1997) and/or Prockop et al (US 2002/0168765).

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of **an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5** (see at least Abstract and Materials and Methods, particularly pages 518-519). The utilized bone marrow stromal support contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop(Science 276:71-74, 1997; see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages**" (see the abstract).

Therefore, the bone marrow stromal cells that were obtained between passages 3 and 5 for transduction as taught by Wells et al are mesenchymal stem cells that have been isolated, purified and culturally expanded from human mesoderm tissue; and that the utilized cell population can be considered to be homogeneous because it is **depleted of hematopoietic cells and macrophages**. Additionally, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Accordingly, the method taught by Wells et al meets every limitation of the claims as broadly written. Therefore, the reference anticipates the instant claims.

(c) Claims 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nolta et al. (Blood 86:101-110, 1995) or Wells et al. (Gene

therapy 2:512-520, 1995) in view of Prockop, D.J. (Science 276:71-74, 1997) and Caplan et al (US 5,486,359).

Nolta et al. disclosed a transduction method for human CD34 cells isolated from bone marrow and peripheral blood with retroviral vectors containing either the bacterial neo gene, or normal human glucocerebrosidase in the presence of a stroma generated by 4th passaged human allogeneic bone marrow stromal cells prior to the plating of CD34 cells (Abstract, and column 1, page 102). **The utilized bone marrow stromal cell population derived from bone marrow spicules is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture** (column 1, third paragraph, page 102). Nolta et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction by vigorous flushing and plating the collected cells twice to eliminate adherent stromal cells (column 1, last paragraph, page 102).

Wells et al. disclosed a transduction method for human bone marrow CD34 progenitor cells from a Gaucher patient with a retroviral vectors containing a normal human glucocerebrosidase cDNA, in the presence of **an autologous bone marrow stromal support containing adherent stromal cells depleted of hematopoietic cells and macrophages that were obtained between passages 3 and 5** (see at least Abstract and Materials and Methods, particularly pages 518-519). Wells et al. further disclosed the isolation of transduced, nonadherent CD34 cells after the transduction (column 1, first full paragraph, page 519).

Neither Nolta et al nor Wells et al teach specifically the use of a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue; **and wherein the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 antigens and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells**.

At the effective filing date of the present application (5/29/1998), Prockop already taught that **bone marrow stromal cells (MSC) can be isolated from other cells in marrow by their tendency to adhere to tissue culture plastic; and that the cells have many of the characteristics of stem cells for tissues that can roughly be defined as mesenchymal because they can be differentiated in culture into osteoblasts, chondrocytes, adipocytes, and even myoblasts** (see at least the abstract). Prockop also noted that **the adherent cells used as feeder layers for HSCs have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of nonadherent cells** (page 72, column 3, bottom of first paragraph). Prockop also disclosed that experiments on the differentiation of MSCs have been carried out with **cultures of MSCs as described by the pioneering work of Friedenstein as well as by other groups that have attempted to prepare more homogeneous populations** (page 72, column 2, top of second paragraph; page 73, column 1, middle of second paragraph).

Additionally, at the effective filing date of the present application **Caplan et al also taught a method of isolating, purifying and culturing expanding human**

mesenchymal stem cells (hMSCs) from bone marrow, including a cell population having greater than 95% of human mesenchymal stem cells that express SH2, SH3 and SH4 antigens (see at least the abstract; col. 1, line 65 continues to line 24 of col. 3; col. 4, lines 36-43). Caplan et al also disclosed **monoclonal hybridoma cell lines that synthesize and secrete monoclonal antibodies specific for human mesenchymal stem cells' SH2, SH3 and SH4 surface antigens; and that these monoclonal antibodies can also be used in the isolation of mesenchymal stem cells though various means** (col. 4, line 64 continues to line 9 of col. 5; col. 14, lines 45-57).

It would have been obvious for an ordinary skilled artisan to modify the teachings of either Nolta et al or Wells et al by also using at least a homogenous population of human bone marrow derived mesenchmal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens, that has been isolated, purified and culturally expanded to support and/or increase gene transduction for human hematopoietic stem cells in light of the teachings of Prockop and Caplan et al as presented above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Prockop already taught that **the adherent cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts.** Moreover, an isolating and purifying method for a homogeneous

population of human bone marrow mesenchymal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens was also taught by Caplan et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Nolta et al or Wells et al; together with the teachings of Prockop and Caplan et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

(10) Response to Argument

(a) Response to arguments for the rejection of claims 3-5 under 35 U.S.C. 102(b) as being anticipated by Nolta et al. (Blood 86:101-110, 1995, Cited previously) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or Prockop et al (US 2002/0168765).

Appellant argues basically that Nolta et al do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded as recited in the instant claims; and that the claimed isolated, purified and then culturally expanded homogeneous population of mesenchymal stem cells is not the same as the cell population taught by Nolta et al. Appellant argues that the result of the isolation technique taught by Nolta et al is a heterogeneous, poorly defined population of marrow derived cells; and nothing in Nolta et al that states that their disclosed

population is a homogeneous population of mesenchymal stem cells, let alone a population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded because the only isolation and purification taught by Nolta et al. is the removal of non-adherent cells by washing the plastic culture plates. Appellant also fails to see the relevancy of the interchangeable use of the terms "Mesenchymal stem cell" and "Marrow stromal cell". Appellant refers the examiner to page 5, lines 1-12 of the instant specification that teach the preparation of a homogeneous population of mesenchymal stem cells as claimed; and the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs). Additionally, Appellant further noted that the present specification differentiates between MSCs and Dexter stroma which is the same as the MDSCs discussed by Majumdar et al. Accordingly, one skilled in the art would recognize that MSCs are a distinct cell population from the heterogeneous stromal cells discussed by Nolta et al. Appellant further argues that Prockop (Science 276:71-74, 1997) does not support the argument that mesenchymal stem cells have been isolated, purified, and culturally expanded since Prockop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Freidenstein" (page 72, col. 1, paragraph 3; and col. 2, paragraph 2).

First, it is noted that **the term "homogeneous" is not defined by the instant specification**; and that a cell population can be 100% homogenous, 90% homogenous, 80% homogenous or even 70% homogeneous. The fact that dependent claim 7 recites

"The method of claim 5, the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells" **indicates clearly that the homogenous population of human mesenchymal stem cells in independent claim 5 can contain cells expressing surface markers for T and B lymphocytes, macrophages, and endothelial cells**. Moreover, the degree of homogeneity of a human mesenchymal stem cell population is also subjective. For example, Prockop et al (US 2002/0168765) taught that **a given mesenchymal stem cell population is far from being homogeneous** (see at least paragraphs 9-18). Sylvester et al (US 7,592,174) stated, "Despite the definitions ascribed to MSC populations by their *in vitro* differentiation capabilities, the mechanisms governing their proliferation and multi-lineage differentiation capacity have been poorly understood...**One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations**...This heterogeneity may be explained by the hypothesis that **true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs**, and the remainder of the mixed population consists of cells at various stages of differentiation and commitment....**There are no universally accepted antigenic determinants of MSC**" (col. 1, line 40 continues to line 16 of col. 2).

Second, it is also noted that the instant specification teaches specifically that human mesenchymal stem cells can be isolated and prepared according to any method

known in the art, **not necessarily limited only to the process of isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture as described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584** (see at least page 5, first paragraph). As written, **the claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method.**

Third, as already set forth in the above rejection the bone marrow stromal cell population derived from bone marrow spicules (after passage no. 4) as taught by Nolta et al. is devoid of most hematopoietic cells (column 1, third paragraph, page 102) and containing mesenchymal stem cells or multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as mesenchymal stem cells or marrow stromal cells (MSCs) (paragraph 2); and "Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages" (see the abstract). **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells at the 4th passage for transfection from an initial split of subconfluent layers of primary stromal cells, Nolta et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells relative at least to collected bone marrow**

specimen and/or primary bone marrow stromal cell culture. Additionally, the utilized 4th passage cell population can be considered to be homogeneous because it is devoid of most hematopoietic cells except for mature macrophages which comprised less than 1% of the culture. Once again, **it is further noted that the dependency of claim 7 on independent claim 5 indicates clearly that the homogeneous population of human mesenchymal stem cells in claim 5 is not necessarily completely free of T and B lymphocytes, macrophages and endothelial cells**. Just because Nolta et al did not use the same term "mesenchymal stem cells", it does not mean that Nolta et al did not teach the same homogenous population of human mesenchymal stem cell encompassed by the instant claims. For example, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can differentiate into multiple non-hematopoietic cell lineages**" (see the abstract). Nolta et al teach the use of **human allogeneic bone marrow stromal cells.**

Fourth, with respect to the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs); it should be noted that **the MDSC cell population of Majumdar et al was prepared by a different protocol from**

that of Nolta et al.; and that the MDSC cells of Majumdar et al. are primary or passage 1 cell culture and not passage 4 cell culture of Nolta et al. Additionally, **the differences seen by Majumdar et al are only for 2 specific cell populations prepared under specific isolation and culture conditions** as evidenced by the statement "**There are several possible explanations for the difference seen in the two cultures, including the methods established for isolation and culture expansion of the cells**. First, MSCs are isolated using Percoll (1.073 g/ml) density sedimentation, while MDSCs were cultured following Ficoll-Paque (1.077 g/ml) fractionation. The small difference in the densities between Percoll and the Ficoll-Paque solutions may be selective for distinct cell populations" (page 63, right column, last paragraph). Once again, **the instant claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method.**

Fifth, the instant specification states explicitly "**Dexter stroma, in addition to MSCs**, contains T and B lymphocytes, macrophages, dendritic cells and endothelial cells" (page 2, lines 7-8). Since **primary Dexter stroma already contained MSCs**, then **selected adherent human bone marrow stromal cell population that is taught by Nolta et al also contains enriched MSCs because it is depleted of hematopoietic cells**. Furthermore, the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in**

Dexter stroma and FN enhanced transduction" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). These statements indicate clearly that **a much less purified, much more heterologous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in the present invention, let alone for the 4th passaged human allogeneic bone marrow stromal cells devoid of most hematopoietic cells taught by Nolta et al**.

Sixth, in contrast to Appellant's above comment regarding to the Prockop reference, Prockop stated explicitly "Therefore, **we used MSCs, prepared as described by Friedenstein and others (5-10)**, from a line of transgenic mice expressing a mutated collagen gene (25)" (page 73, col. 1, middle of the second paragraph).

(b) Response to arguments for the rejection of claims 2 and 4-5 under 35 U.S.C. 102(b) as being anticipated by Wells et al. (Gene therapy 2:512-520, 1995) as evidenced by Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and/or Prockop et al (US 2002/0168765).

Once again, Appellant argues basically that Wells et al do not teach a homogenous population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded as recited in the instant claims; and that the claimed isolated, purified and then culturally expanded homogeneous population of mesenchymal stem cells is not the same as the cell population taught by Wells et al.

Appellant argues that the result of the isolation technique taught by Wells et al is a heterogeneous, poorly defined population of marrow derived cells; and nothing in Wells et al that states that their disclosed population is a homogeneous population of mesenchymal stem cells, let alone a population of mesenchymal stem cells that have been isolated, purified, and then culturally expanded. Appellant also fails to see the relevancy of the interchangeable use of the terms "Mesenchymal stem cell" and "Marrow stromal cell". Appellant also refers the examiner to page 5, lines 1-12 of the instant specification that teach the preparation of a homogeneous population of mesenchymal stem cells as claimed; and the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs). Additionally, Appellant further noted that the present specification differentiates between MSCs and Dexter stroma which is the same as the MDSCs discussed by Majumdar et al. Accordingly, one skilled in the art would recognize that MSCs are a distinct cell population from the heterogeneous stromal cells discussed by Wells et al. Appellant further argues that Prockop (Science 276:71-74, 1997) does not support the argument that mesenchymal stem cells have been isolated, purified, and culturally expanded since Prockop teaches that there are advantages to utilizing isolation and purification methods as opposed to the "crude procedure of Freidenstein" (page 72, col. 1, paragraph 3; and col. 2, paragraph 2).

First, it is noted that **the term "homogeneous" is not defined by the instant specification**; and that a cell population can be 100% homogenous, 90% homogenous,

80% homogenous or even 70% homogeneous. The fact that dependent claim 7 recites "The method of claim 5, the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells" **indicates clearly that the homogenous population of human mesenchymal stem cells in independent claim 5 can contain cells expressing surface markers for T and B lymphocytes, macrophages, and endothelial cells**. Moreover, the degree of homogeneity of a human mesenchymal stem cell population is also subjective. For example, Prockop et al (US 2002/0168765) taught that **a given mesenchymal stem cell population is far from being homogeneous** (see at least paragraphs 9-18). Sylvester et al (US 7,592,174) stated, "Despite the definitions ascribed to MSC populations by their *in vitro* differentiation capabilities, the mechanisms governing their proliferation and multi-lineage differentiation capacity have been poorly understood...**One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations**...This heterogeneity may be explained by the hypothesis that **true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs**, and the remainder of the mixed population consists of cells at various stages of differentiation and commitment....**There are no universally accepted antigenic determinants of MSC**" (col. 1, line 40 continues to line 16 of col. 2).

Second, it is noted that the instant specification teaches specifically that human mesenchymal stem cells can be isolated and prepared according to any method known in the art, **not necessarily limited only to the process of isolating, purifying, and expanding the marrow-derived mesenchymal stem cells in culture as described in U.S. Patent Nos. 5,197,985 and 5,226,914 and PCT Publication No. WO 92/22584** (see at least page 5, first paragraph). As written, **the claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method.**

Third, as already set forth in the above rejection **an autologous bone marrow stromal support depleted of hematopoietic cells and macrophages, and obtained between passages 3 and 5** by Wells et al contains isolated mesenchymal stem cells or isolated multipotential bone marrow stromal cells (MSCs) as evidenced by the teachings of Prockop (Science 276:71-74, 1997; see at least the abstract; and particularly page 72, col. 3), including the disclosure that the adherent cells used as feeder layers for hematopoietic stem cells have many of the characteristics of MSCs isolated by their adherence to plastic in the absence of non-adherent cells. Furthermore, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that can**

differentiate into multiple non-hematopoietic cell lineages" (see the abstract). **By passaging bone marrow stromal cells and collected adherent bone marrow stromal cells between passages 3 and 5 for transfection from an initial split of subconfluent layers of primary stromal cells, Wells et al in fact isolated, purified and culturally expanded bone marrow stromal cells or mesenchymal stem cells relative at least to collected bone marrow specimen and/or primary bone marrow stromal cell culture. Additionally, the utilized cell population between passages 3 and 5 can be considered to be homogeneous because it is depleted of hematopoietic cells and macrophages**. Once again, **it is further noted that the dependency of claim 7 on independent claim 5 indicates clearly that the homogeneous population of human mesenchymal stem cells in claim 5 is not necessarily completely free of T and B lymphocytes, macrophages and endothelial cells**. Just because Wells et al did not use the same term "mesenchymal stem cells", it does not mean that Wells et al did not teach the same homogenous population of human mesenchymal stem cell encompassed by the instant claims. For example, the terms "Mesenchymal stem cell" and "Marrow stromal cell" have been used interchangeably in the art as also evidenced at least by the teachings of Prockop et al (US 2002/0168765) who stated, "Bone marrow contains at least two kinds of stem cells, hematopoietic stem cells and stem cells for non-hematopoietic tissues (1-27) variously referred to as **mesenchymal stem cells or marrow stromal cells** (MSCs) (paragraph 2); and "**Marrow stromal cells (MSCS) are adult stem cells from bone marrow that**

can differentiate into multiple non-hematopoietic cell lineages" (see the abstract). Wells et al teach the use of **human autologous bone marrow stromal cells.**

Fourth, with respect to the post-filing art of Majumdar et al (J. Cell. Phys. 178:57-66, July 1998) which showed the differences between isolated, purified mesenchymal stem cells and marrow-derived stromal cells (MDSCs); it should be noted that **the MDSC cell population of Majumdar et al was prepared by a different protocol from that of Wells et al.; and that the MDSC cells of Majumdar et al. are primary or passage 1 cell cultures and not bone marrow stromal cell culture between passages 3 and 5 of Wells et al**. Additionally, **the differences seen by Majumdar et al are only for 2 specific cell populations prepared under specific isolation and culture conditions** as evidenced by the statement "**There are several possible explanations for the difference seen in the two cultures, including the methods established for isolation and culture expansion of the cells**. First, MSCs are isolated using Percoll (1.073 g/ml) density sedimentation, while MDSCs were cultured following Ficoll-Paque (1.077 g/ml) fractionation. The small difference in the densities between Percoll and the Ficoll-Paque solutions may be selective for distinct cell populatons" (page 63, right column, last paragraph). Once again, **the instant claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method.**

Fifth, the instant specification states explicitly "**Dexter stroma, in addition to MSCs**, contains T and B lymphocytes, macrophages, dendritic cells and endothelial cells" (page 2, lines 7-8). Since **primary Dexter stroma already contained MSCs**,

then **selected adherent human bone marrow stromal cell population that is taught by Wells et al also contains enriched MSCs because it is depleted of hematopoietic cells and macrophages**. Furthermore, the instant specification states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). These statements indicate clearly that **a much less purified, much more heterologous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in the present invention, let alone for human autologous bone marrow stromal cells between passages 3 and 5, and depleted of hematopoietic cells and macrophages as taught by Wells et al**.

Sixth, in contrast to Appellant's above comment regarding to the Prockop reference, Prockop stated explicitly "Therefore, **we used MSCs, prepared as described by Friedenstein and others (5-10)**, from a line of transgenic mice expressing a mutated collagen gene (25)" (page 73, col. 1, middle of the second paragraph).

(c) Response to arguments for the rejection of 5 and 7 under 35 U.S.C. 103(a) as being unpatentable over either Nolta et al. (Blood 86:101-110, 1995,

Cited previously) or Wells et al. (Gene therapy 2:512-520, 1995) in view of Prockop, D.J. (Science 276:71-74, 1997; Cited previously) and Caplan et al (US 5,486,359).

1. Appellant argues basically that the Office has failed to provide a reasonable rationale to combine either Nolta et al or Wells et al with Prockop and Caplan et al to teach transforming human hematopoietic progenitor cells in the presence of isolated, purified, and culturally expanded human mesenchymal stem cells. Appellant also failed to see the relevance of the motivation statement set forth in the rejection as to why one skilled in the art would use a homogenous population of mesenchymal stem cells for co-culturing human hematopoietic cells that are transformed; and that the statement does not provide a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. Additionally, Appellant argues that it has been held that a claimed composition would have not been obvious where there was no reason to modify the closest prior art composition to obtain the claimed composition and the prior art taught that modifying the closest prior art would destroy its advantageous properties. In this instance, Appellant argues that neither Nolta et al nor Wells et al provide any teaching that a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue would be desirable to use compared to other isolated cell populations derived from bone marrow. Therefore, the Examiner has not identified any reason which would have

prompted an ordinary artisan to select a population of isolated, purified, and culturally expanded human mesenchymal stem cells.

First, once again it is noted that **the term "homogeneous" is not defined by the instant specification**; and that a cell population can be 100% homogenous, 90% homogenous, 80% homogenous or even 70% homogeneous. The fact that dependent claim 7 recites "The method of claim 5, the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 surface antigens, and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells" **indicates clearly that the homogenous population of human mesenchymal stem cells in independent claim 5 can contain cells expressing surface markers for T and B lymphocytes, macrophages, and endothelial cells**. Moreover, the degree of homogeneity of a human mesenchymal stem cell population is also subjective. For example, Prockop et al (US 2002/0168765) taught that **a given mesenchymal stem cell population is far from being homogeneous** (see at least paragraphs 9-18). Sylvester et al (US 7,592,174) stated, "Despite the definitions ascribed to MSC populations by their *in vitro* differentiation capabilities, the mechanisms governing their proliferation and multi-lineage differentiation capacity have been poorly understood...**One of the greatest obstacles in the study of MSC biology is the heterogeneity of studied cell populations**...This heterogeneity may be explained by the hypothesis that **true "mesenchymal stem cells" (cells with the ability to self-renew and differentiate into multiple lineages) are only a small sub-population of the pool of cells termed MSCs**, and the remainder of the mixed population consists of

cells at various stages of differentiation and commitment....**There are no universally accepted antigenic determinants of MSC**" (col. 1, line 40 continues to line 16 of col. 2). Furthermore, **the claims also do not limit a homogenous population of human mesenchymal stem cells to be isolated, purified and culturally expanded by any particularly method** Please also **refer to the Examiner's additional responses** to Appellant's arguments on the issue that neither Nolta et al nor Wells et al provide any teaching that a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue as already set forth above.

Second, the teachings of Prockop and Caplan et al supplement the teachings of either Nolta et al or Wells et al since none of these primary references teaches specifically the use of a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue; **and wherein the homogenous population of mesenchymal stem cells uniformly expressing SH2, SH3, and SH4 antigens and lacking surface markers for T and B lymphocytes, macrophages, and endothelial cells**. As already set forth in the above 103 rejection, an ordinary skilled artisan would have been motivated to modify the teachings of either Nolta et al or Wells et al by also **using at least a more homogenous population of human bone marrow derived mesenchmal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens, that has been isolated, purified and culturally expanded to support and/or increase gene transduction for human hematopoietic stem cells** because Prockop already noted that **the adherent**

cells used as feeder layers for HSCs have many of the characteristics of bone marrow stromal cells that are characterized by their tendency to adhere to tissue culture plastic and are capable of differentiating into osteoblasts, chondrocytes, adipocytes, and even myoblasts; and **an isolating and purifying method for a more homogeneous population of human bone marrow mesenchymal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens** was already taught successfully by Caplan et al. Since either Nolta et al or Wells et al already successfully used a human bone marrow stromal cell population or a mesenchymal stem cell population to support the transduction of human bone marrow CD34+ stem cells in the presence of a recombinant retroviral vector, **it would have been obvious that an ordinary skilled artisan could also use a more homogeneous population of human bone marrow mesenchymal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens for the same application**.

2. Appellant argues that one of ordinary skill in the art would not find it predictable and/or have a reasonable expectation of success of transforming hematopoietic progenitor cells to express a protein by co-culturing human hematopoietic progenitor cells with a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue. Appellant argues that Nolta et al and Wells et al merely teach methods for transduction of hematopoietic stem cells on stromal feeder cells and do not specifically teach the use of a homogenous population of human mesenchymal stem cells that have been isolated, purified and then culturally expanded from human mesoderm tissue;

while Prockop teaches at the time of the filing of the present application that it was unknown which "more homogenous" populations of isolated marrow stromal cells retained any of the characteristics of the crude heterogeneous populations described by Friedenstein. Additionally, Prockop does not teach that any of the potential isolated cell types are the MSCs of the present invention nor has the Examiner presented any evidence that a skilled artisan would predict successful transduction using the more homogenous populations of marrow stem cells. With respect to the Caplan et al reference, Appellant argues that the reference does not teach that the human mesenchymal stem cells would be effective in a method for transforming hematopoietic progenitor cells to express a protein nor the Examiner has presented any evidence that the MSCs of the present invention had an established function in HSC transduction at the filing date of the present application.

First, there is nothing that is unpredictable or unexpected for the method as claimed. This is because both Nolta et al and Wells et al already successfully demonstrated the use of **the 4th passage human allogeneic bone marrow stromal cell population and the autologous human bone marrow stromal cell population (obtained between passages 3 and 5) depleted of hematopoietic cells and macrophages; respectively,** and **which contains a homogenous population of human mesenchymal stem cells as already discussed extensively above** to support the transduction of human bone marrow CD34+ stem cells in the presence of a recombinant retroviral vector**.** Then; a more homogenous human bone marrow mesenchymal stem cells expressing uniformly SH2, SH3 and SH4 surface antigens

would also be reasonably expected to support the transduction of human bone marrow CD34+ stem cells in the presence of a recombinant retroviral vector. The examiner' position is further supported by the instant specification which states specifically "These results demonstrate that hMSCs are able to support ex vivo gene transfer into CD34 human hematopoietic progenitor cells **that exhibit transduction efficiencies, cell expansion and drug resistance properties comparable to the levels produced in Dexter stroma and FN enhanced transduction**" (page 13, lines 23-26)., and that **Dexter stroma was derived from adhered bone marrow mononuclear cells that were passaged once** (page 10, lines 12-23). These statements indicate clearly that **a much less purified, much less homogenous Dexter stromal cells (passaged only once) was already shown to be at least functionally equivalent to hMSCs used in the present invention.**

Second, it is noted that Prockop stated explicitly "Therefore, **we used MSCs, prepared as described by Friedenstein and others (5-10)**, from a line of transgenic mice expressing a mutated collagen gene (25)" (page 73, col. 1, middle of the second paragraph). **This statement indicates that at the filing date of the present application, a skilled artisan could prepare MSCs by various methods, including the "crude" method of Friedenstein**.

Third, since the rejection was made under 35 U.S.C. 103(a) none of the cited references has to teach every limitation of the instant claims. In this instance, the Caplan et al reference does not have to teach that human mesenchymal stem cells would be effective in a method for transforming hematopoietic progenitor cells to

express a protein. It also appears that Appellant argue the Caplan et al reference in total isolation from the teachings of Nolta et al, Wells et al and Prockop.

Fourth, it is noted that human mesenchymal stem cells of the present application were isolated by simply collecting mononuclear cells at the interface after a Percoll (1.073 g/ml) density centrifugation at 900 x g for 30 minutes (see example).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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